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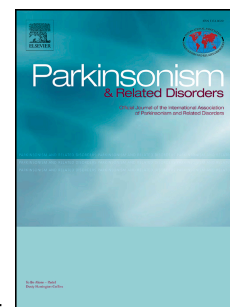
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Stimulation of the globus pallidus internus in the treatment of Parkinson's disease: long-term results of a monocentric cohort

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Abstract

Background: Pallidal deep brain stimulation (DBS) has shown to be beneficial in patients with advanced levodopa-responsive Parkinson's disease (PD) in several short-term studies. However, reported long-term outcomes of pallidal DBS for PD are limited and contradictory.

Methods: Eighteen consecutive PD patients were treated with unilateral or bilateral stimulation of the internal part of the globus pallidus (GPi). Assessments were carried out before and six months after neurosurgery, and annually thereafter for up to 16 years (mean follow-up time: 6 years). Primary outcomes included motor signs (Unified PD Rating Scale [UPDRS]-III), activities of daily living (ADL, UPDRS-II), and levodopa-induced motor complications (UPDRS-IV).

Results: The results show that GPi stimulation improves levodopa responsive PD motor signs (UPDRS-III), levodopa-induced motor complications (UPDRS-IV), and ADL (UPDRS-II) in advanced PD. Among motor signs, tremor showed the best response to pallidal stimulation. Levodopa-induced motor complications and tremor showed improvements for more than 10 years after neurosurgery.

Conclusions: The overall findings in our cohort demonstrate that pallidal stimulation is effective in reducing parkinsonian motor signs (UPDRS-III), particularly in the 'off'-medication state. Although the beneficial effects on bradykinesia, rigidity and ADL may be limited to 5 to 6 years, the follow up results indicate that the improvements of levodopa-induced motor complications (UPDRS-IV) and tremor can be sustained for more than 10 years.

Introduction

Deep brain stimulation (DBS) of the internal part of the globus pallidus (GPi) is beneficial in patients with advanced levodopa-responsive Parkinson's disease (PD) with significant improvement of tremor, bradykinesia, rigidity, gait, postural stability, levodopa-induced motor fluctuations, and dyskinesia in the first year after surgery [1-8]. However, reported long-term outcomes (>24 months post-surgery) of pallidal DBS for PD are limited and contradictory. While some follow-up studies indicate that the initial response to stimulation might disappear in the aftermath [3, 7, 9-11], others report a sustained improvement for up to 3-4 [12-17] or 6 years [18] after surgery. Here, we report on long-term results (up to 16 years) in a cohort of 18 PD patients treated with pallidal DBS and prospectively followed at the University Hospital of Bern.

Patients

Our cohort is a consecutive series of 18 patients (11 male and 7 female; mean age at time of surgery 64.8 ± 7.4 years) with advanced PD (mean disease duration at time of surgery 16.2 ± 6.8 years) who received unilateral ($n=4$) or bilateral ($n=14$) electrode implantations for DBS of the GPi at the University Hospital of Bern. The selection criteria for neurosurgery included: (i) advanced PD; (ii) good response to levodopa; (iii) medication-refractory motor fluctuations and levodopa-induced dyskinesia despite best medical treatment; (iv) absence of neurosurgical contraindications. Eleven patients received electrode implantation in the late 1990s, when only GPi-DBS was performed at the University Hospital Bern. STN-DBS was introduced later and then became the preferred target for patients with normal cognition and without levodopa-resistant axial motor signs. Detailed patient characteristics are shown in

table 1. All patients provided consent for follow-up evaluations. The mean follow-up time was 6 years (range 1 to 16 years). The variance of follow up time is due to different time points of implantation and loss of follow up. During the observation period (1997 to 2015) six patients were lost for follow up due to death, one patient due to a spontaneous cerebral haemorrhage, one patient because of a change of residence, two patients because of unknown reasons and one patient denied further follow up visits.

Methods

The surgical procedure was performed as previously reported [6]. All patients underwent postoperative axial computed tomography (CT) to monitor complications and verify electrode position. Correct electrode position was documented by the neurosurgeon for all patients. Lead position was retrospectively checked for seven patients by co-registration of the postoperative CT with preoperative T2-weighted magnetic resonance imaging (MRI) and showed no active contact outside the GPi. However, for eleven patients who received electrode implantation in the late 1990s, no digital CT scans were available for determination of lead position. Postoperatively, stimulation settings and antiparkinson medication were gradually adapted based on patient need and clinical response.

All patients underwent standardized clinical evaluations before and six months after neurosurgery, and annually thereafter as part of their routine long-term care. These evaluations included application of the Unified Parkinson's Disease Rating Scale (UPDRS) [19] during both 'off'- and 'on'-medication periods, the Schwab and England scale of activities of daily living [20], the Mini-Mental Status Examination (MMSE) [21] and the Hamilton Depression Scale (HAM-D21) [22]. All motor assessments were videotaped.

The assessments were performed after an overnight withdrawal of antiparkinsonian medication in a defined 'off'-drug condition, and in the best 'on'-drug condition after administration of levodopa. During each visit, information on the dosage of levodopa and other antiparkinsonian drugs as well as stimulation parameters were obtained. Furthermore, technical failures were ruled out by measurements of impedance and battery load.

Video motor assessments were scored by an independent rater in a blinded condition with the UPDRS part III, with the exception of rigidity. Comparison of blinded versus unblinded UPDRS-III assessments showed good agreement with an average difference of 3 UPDRS points (Bland-Altman plot). Therefore, the unblinded assessments that included ratings for rigidity were used for further statistical analysis. The analysis was exploratory and included all evaluable patients. No missing values were imputed. The two-sided Wilcoxon signed-rank test was used for paired comparisons of baseline and follow-up examinations. P-values <0.05 were considered significant and no correction for multiple testing was applied. Statistical analysis of treatment efficacy compared to baseline was conducted for the follow up assessments at ≤ 1.5 years, $1.5 \leq 3.5$ years, $3.5 \leq 5.5$ years, ≥ 5.5 years and 10 years. Authorization to perform the analysis was granted by the institutional review board (local ethics committee).

Results

Motor signs

UPDRS-III score in the 'off-medication/on-stimulation' condition was significantly improved by 26% ($p=0.001$; $n=17$) 1.5 years after surgery and after 5.5 years by 22% ($p=0.027$; $n=10$) when compared to baseline before surgery ($n=18$) (Fig.1A). However, after 10 years ($n=4$), UPDRS-III almost reached baseline score (Tab.2). Tremor

showed the best response to pallidal stimulation (Fig. 1B), and this improvement (55%) was significantly sustained for >5.5 years after surgery ($p=0.039$; $n=8$) and even present (44%) 10 years after surgery ($n=4$; only descriptive statistics presented) (Tab.2). Rigidity was significantly improved by 24% up to 5.5 years ($p=0.043$; $n=10$), while beneficial effects on bradykinesia disappeared within 3.5 to 5.5 years (Fig.1C+D; Tab.2). 'Axial' signs, defined as the sum of the motor subscores for speech, gait, posture and postural stability (items 18, 27, 28, 29 and 30 of the UPDRS-III) were significantly improved by 19% ($p=0.002$; $n=17$) up to 3.5 years after surgery (Fig.1E; Tab.2) and showed a trend towards improvement up to 5.5 years ($p=0.075$; $n=10$). In the 'on-medication/on-stimulation' condition, the UPDRS-III score showed no improvement compared to baseline, but significant worsening after 5.5 years ($p=0.035$) (Tab.2).

Motor complications

Levodopa-induced motor complications assessed with the UPDRS-IV were significantly improved by about 50% up to 5.5 years after surgery ($p=0.005$; $n=10$) and remained improved by 41% even >5.5 years after surgery ($p=0.007$; $n=8$). Ten years after surgery the UPDRS-IV was still improved by 26% ($p=NA$; $n=4$) (Fig.1G; Tab.2). Dyskinesia (UPDRS-IV items 32-34) were significantly improved for >5.5 years after surgery by 49% ($p=0.007$) (Fig.1H) and remained improved 10 years after surgery (22%). This improvement applied both to duration (item 32) and disability (item 33) (Tab.2). Motor fluctuations (UPDRS-IV items 36-39) were significantly improved for >5.5 years after surgery by 38% ($p=0.035$) (Fig.1I) and remained improved 10 years after surgery by 26% ($p=NA$; $n=4$) (Tab.2).

Activities of daily living (ADL)

UPDRS-II was significantly improved by 28% ($p < 0.001$; $n = 17$) 1.5 years after surgery, remained improved after 3.5 years by 21% ($p = 0.007$; $n = 17$), and showed a trend towards improvement ($p = 0.082$; $n = 10$) up to 5.5 years after surgery (Fig.1F, Tab.2). The Schwab and England scale consistently showed significant improvement of ADL up to 3.5 years after surgery ($p = 0.034$) (Tab.2).

Mood

GPI-DBS significantly improved depression scores compared to pre-operative baseline, with the average HAM-D21 score decreasing from 7.8 ± 5.0 (mean \pm SD) to $4.5 \pm 2.8.0$ ($p = 0.002$) up to 3.5 years (Tab.2). A linear regression model adjusted for the duration of follow-up identified a significant negative relationship between baseline score and change at the last visit (coefficient -0.91; $p < 0.001$ - Fig.1K).

Levodopa equivalent daily dose (LEDD)

Daily levodopa equivalent dose at the last postoperative follow up compared with baseline was stable on average (1102 ± 472 mg at baseline and 1161 ± 346 mg at last follow up, $p = 0.22$), but had to be increased over time in some patients.

Stimulation settings

The average parameters were 2.1 ± 1.0 V amplitude, 176.3 ± 52.9 μ s pulse width, and 128.6 ± 34.9 Hz frequency. Eighteen electrodes were stimulated in monopolar, ten in bipolar, and four in double monopolar mode.

Case of longest follow up

One patient with early onset PD (age 34 at onset), who received DBS implantation 20 years after disease onset, showed a preserved levodopa-response over decades and

improvement of UPDRS-III (30%), UPDRS-IV (20%) and UPDRS-II (26%) 16 years after surgery (Fig.2A-C). Analysis of UPDRS-III subscores revealed a remarkable improvement of tremor and, to a lesser extent, bradykinesia, which was preserved over 16 years (Fig.2A-C; Video). One year after initial DBS implantation, electrodes were repositioned because of dislocation.

Adverse effects

There were no intraoperative complications. Device related complications occurred in seven of the patients during the observation time and required surgical intervention. Reasons for surgical interventions were once a dislocation with subsequent reposition of electrodes; three times a broken cable or lead; twice an infection of the wound, in one of these cases the battery and cables had to be removed and were later replaced; once a seroma, which led to a revision and change of the pulse generator. One patient suffered a spontaneous cerebral haemorrhage in the thalamus 33 months after surgery with consecutive hemiparesis. Another patient developed transient psychosis 3 weeks after surgery. None of the patients suffered from permanent deficits related to the procedure.

Discussion

Our study confirms the effectiveness of GPi-DBS in improving levodopa-responsive PD motor signs, levodopa-induced motor complications, and ADL in advanced PD. These findings are consistent with other studies that suggest a robust improvement in motor signs and levodopa-induced dyskinesia after one year [1-6, 23-26].

In addition, our long-term follow-up results show that motor benefit (UPDRS-III) is sustained in the 'off-medication/on-stimulation' up to 5.5 years after surgery, which is

in line with other reports that describe stable responses over time [12-18]. In particular, tremor was significantly improved in our patients >5.5 years after surgery and this benefit was retained even 10 years after surgery. However, statistical analysis was not applicable due to the low number of patients (n=4). The beneficial effect for bradykinesia disappeared after 3.5 years and for rigidity and axial motor signs after 5.5 years. This decline might be related to the natural progression of PD as indicated by the worsening of UPDRS-III score in the 'on-med/on-stim condition' after 5.5 years compared to the baseline score in the 'on-med condition'. Despite the worsening of the UPDRS-III score, the mean LEDD was stable, which can either be due to the appearance of levodopa resistant motor signs as it is common in advanced PD, or to suboptimal dosage of prescribed daily dopaminergic medications. As annual levodopa challenge tests were performed with the aim to identify a dopaminergic reserve to optimize medical treatment in our patients, we think under-dosing with levodopa is a less likely explanation. Moreover, stable LEDD has also been reported by other long-term GPi-DBS studies [7, 13].

Although MMSE scores decreased over time, no statistically significant cognitive worsening was noted (Tab.2). This might be explained by the small sample size, but also by the low sensitivity of the MMSE to detect early and mid-stage cognitive changes that occur in PD, as the MMSE assesses more amnesic and language-based than executive functions [27]. Furthermore, no persistent DBS-related serious adverse effects were observed in the follow-up, providing further evidence for long-term safety/tolerability of pallidal stimulation. Motor complications have been assessed by history taking and quantified in the UPDRS-IV. However, as patient diaries were not used, we cannot estimate the number of hours per day spent with or without dyskinesia. Nevertheless, levodopa-induced motor complications assessed by the UPDRS-IV were significantly improved for more than 5.5 years. This improvement

accounted equally for levodopa induced dyskinesia and motor fluctuations and was maintained for 10 years, confirming the sustained efficacy of pallidal stimulation in the treatment of PD with levodopa-induced motor complications. In a single case with early onset PD and preserved levodopa-response over the years, clinically relevant improvement of motor signs, levodopa-induced motor complications, and ADL remained even 16 years after surgery. The fact that this patient had a 20-year PD history prior to implantation could indicate a very slow progression of the disease and therefore limits the generalizability of this example to the average PD case with pallidal DBS.

This study has several limitations. First, the statistical power was limited due to the small number of patients. This implies that statistically non-significant results are difficult to interpret. In addition, false positive findings cannot be excluded, so statistical tests can only have exploratory value. Second, 4 of the 18 patients had only unilateral pallidal stimulation, but statistical analysis of patients with only bilateral pallidal stimulation revealed similar results, though less significant due to the smaller sample size. Moreover, in 11 patients the available imaging does not permit an exact localization of the therapeutic leads within the target. Therefore, variability of targeting may contribute to the differences in the outcome. Although subthalamic nucleus DBS became available at our centre while the last 7 patients of this series were operated, the therapy decision remained unaffected by the availability of STN-DBS. Finally, the length of the follow-up period was variable due to the different time points of implantation and loss of follow up. Therefore, no statistical analysis has been performed for the follow-up data after 10 years (n=4).

In summary, pallidal DBS is effective in reducing parkinsonian motor signs, but beneficial effects on bradykinesia and rigidity may be limited to 5 to 6 years. However, our

long-term results show for the first time that the remarkable improvements of levodopa-induced motor complications and tremor were sustained for up to 10 years and in a single case for 16 years, confirming the long-term efficacy of GPi-DBS in advanced PD. Although 'off'-drug phase motor improvement might be greater after STN-DBS [28, 29], our findings indicate that the GPi is a viable DBS target for treatment of PD motor signs and levodopa-induced motor complications with a sustained effect.

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characteristics	
number of patients	18
gender	11 male, 7 female
Age at time of surgery	64.8 \pm 7.4
Age at onset illness	48.6 \pm 8.5
Duration of Parkinson's disease	16.2 \pm 6.8
UPDRS II	
OFF	26.3 \pm 8.5
ON	16.4 \pm 4.8
UPDRS III	
OFF	50.6 \pm 16.4
ON	25.3 \pm 9.0
UPDRS IV	13.4 \pm 2.5
Schwab&England	
OFF	42.8 \pm 16.4
ON	69.4 \pm 17.3
LEDD (mg)	1102 \pm 472

Table 1. Baseline characteristics of patients. Values are means \pm SD.

		Baseline		Year <=1.5				Year 1.5 - <=3.5				Year 3.5 - <=5.5				Year >5.5				Year 10				
	item	score	n	score	n	delta (%)	p-value	score	n	delta (%)	p-value	score	n	delta (%)	p-value	score	n	delta (%)	p-value	score	n	delta (%)	p-value	
	UPDRS-II OFF	5-17	26.3±8.5	18	18.8±5.6	17	-28	<0.001	20.6±5.2	17	-21	0.007	21.2±4.1	10	-19	0.0828	24.2±4.2	8	-8	0.1609	23.2±5.5	4	-12	NA
	UPDRS-III OFF-MED ON-STIM	18-31	50.6±16.4	18	37.3±10.5	17	-26	0.0016	40.6±13.1	17	-20	0.0015	39.3±9.3	10	-22	0.0273	47.1±8.3	8	-7	0.207	52.2±9.3	4	3	NA
	tremor	20, 21	6.3±4.7	18	3.6±3.4	17	-43	<0.001	3.7±3.4	17	-41	0.0021	2.8±3.3	10	-55	0.009	2.8±2.3	8	-55	0.0391	3.5±1.9	4	-44	NA
	rigidity	22	8.9±4.4	18	7.2±2.9	17	-19	0.0059	7.7±3.3	17	-13	0.0779	6.7±2.5	10	-24	0.0436	8.5±4.1	8	-4	0.1829	10.5±1.0	4	15	NA
	bradykinesia	19, 23-26, 31	22.8±6.7	18	17.3±4.5	17	-24	0.0069	18.7±6.6	17	-18	0.0077	20.6±5.9	10	-9	0.5519	23.6±3.8	8	3	0.999	26.8±5.3	4	15	NA
	axial signs	18, 27-30	12.7±3.8	18	9.1±3.6	17	-28	0.0052	10.3±3.4	17	-19	0.0024	9.2±3.1	10	-27	0.0756	12.1±3.2	8	-5	0.3096	11.5±4.4	4	-9	NA
	UPDRS-III ON-MED ON-STIM	18-31	25.3±9.0	18	20.5±7.3	17	-19	0.0797	22.6±8.2	17	-11	0.1181	26.7±7.0	10	5	0.999	35.3±7.9	8	28	0.0355	33.7±2.3	4	25	NA
	UPDRS-IV	32-42	13.4±2.5	18	6.6±2.5	17	-51	<0.001	6.6±2.7	17	-51	<0.001	6.5±3.5	10	-51	0.005	7.9±3.9	8	-41	0.0078	9.8±5.9	4	-26	NA
	dyskinesia	32-34	4.9±2.3	18	1.8±1.4	17	-63	<0.001	2.0±1.6	17	-59	<0.001	1.9±1.7	10	-61	0.0057	2.5±2.0	8	-49	0.0078	3.8±3.2	4	-22	NA
	duration	32	2.5±1.0	18	1.1±0.7	17	-56	<0.001	1.3±1.1	17	-48	0.0028	1.2±0.7	10	-52	0.0133	1.4±0.8	8	-44	0.0418	1.8±1.0	4	-28	NA
	disability	33	2.9±0.9	18	0.7±0.8	17	-76	<0.001	0.9±0.9	17	-69	0.001	1.0±0.9	10	-66	0.0124	1.6±0.8	8	-45	0.022	2.0±0.8	4	-31	NA
	fluctuations	36-39	4.7±0.8	18	3.1±1.3	17	-34	0.001	3.0±1.1	17	-36	0.0031	2.7±1.3	10	-43	0.0084	2.9±1.6	8	-38	0.0355	3.5±1.9	4	-26	NA
	Schwab&England OFF	-	42.8±16.4	18	51.5±16.0	17	17	0.0024	49.7±12.1	17	14	0.0344	51.8±14.0	10	17	0.1248	45.9±12.7	8	8	0.2807	32.5±15	4	-24	NA
	HAM-D21	-	7.8±5.0	18	5.3±3.1	17	-32	0.0168	4.5±2.8	17	-26	0.0024	5.8±4.0	10	-25	0.0827	6.6±4.7	8	-15	0.2049	3.3±2.3	3	-57	NA
	MMSE	-	26.6±3.1	18	26.7±3.0	17	0	0.9621	24.6±6.4	17	-8	0.6412	24.9±4.3	10	-6	0.677	24.1±3.5	8	-9	0.1829	22.8±7.6	3	-14	NA

Table 2. UPDRS-II-IV, Schwab and England, Hamilton-Depression-Scale (HAM-D21) and Mini-Mental Status Examination (MMSE) before and after neurosurgery. Values are means (\pm SD). n = number of patients. delta = mean percentage change in comparison to the baseline.

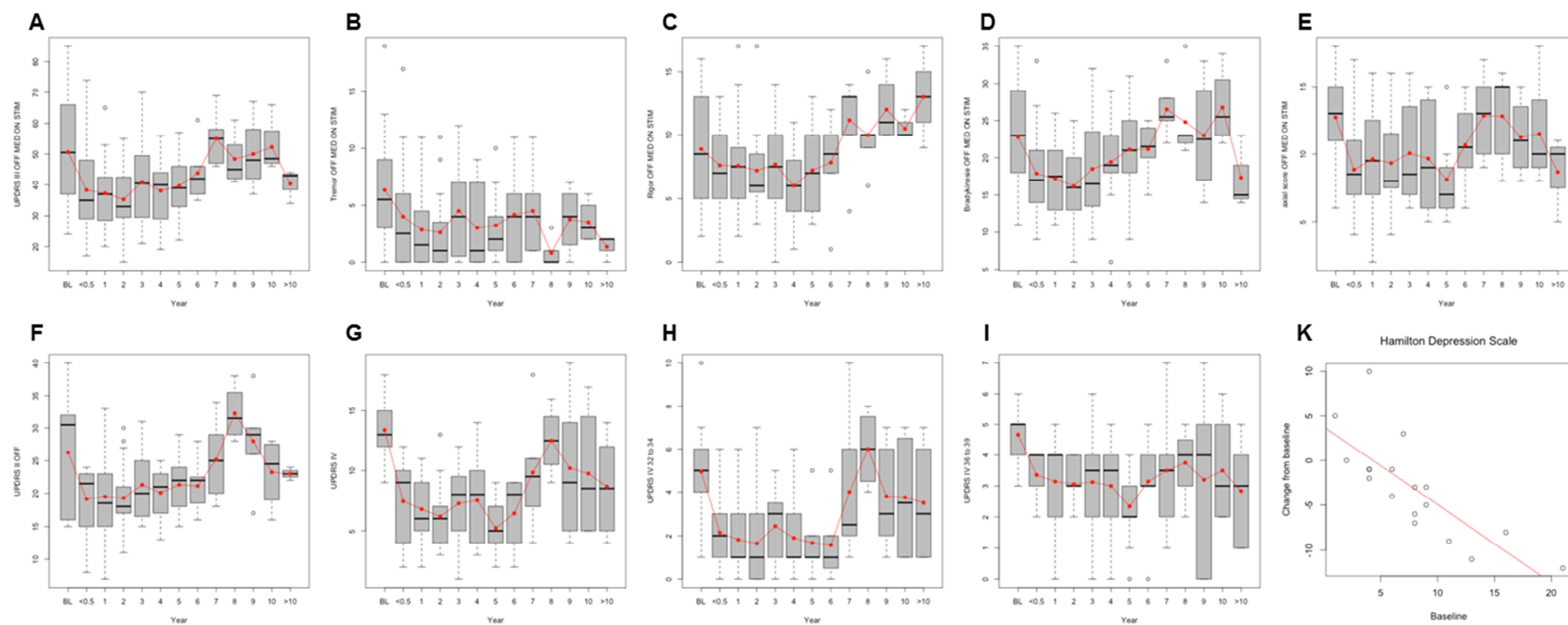


Figure 1. Boxplots of (A) UPDRS-III, (B-E) UPDRS-III subscores, (F) UPDRS-II in the off medication condition and (G) UPDRS-IV and (H, I) UPDRS-IV subscores. Scatter plot of (K) HAM-D21 score change versus baseline score; linear regression model: change ~ baseline ~ duration of observation period; multiple R-Squared: 0.62289, $p=0.0007$.

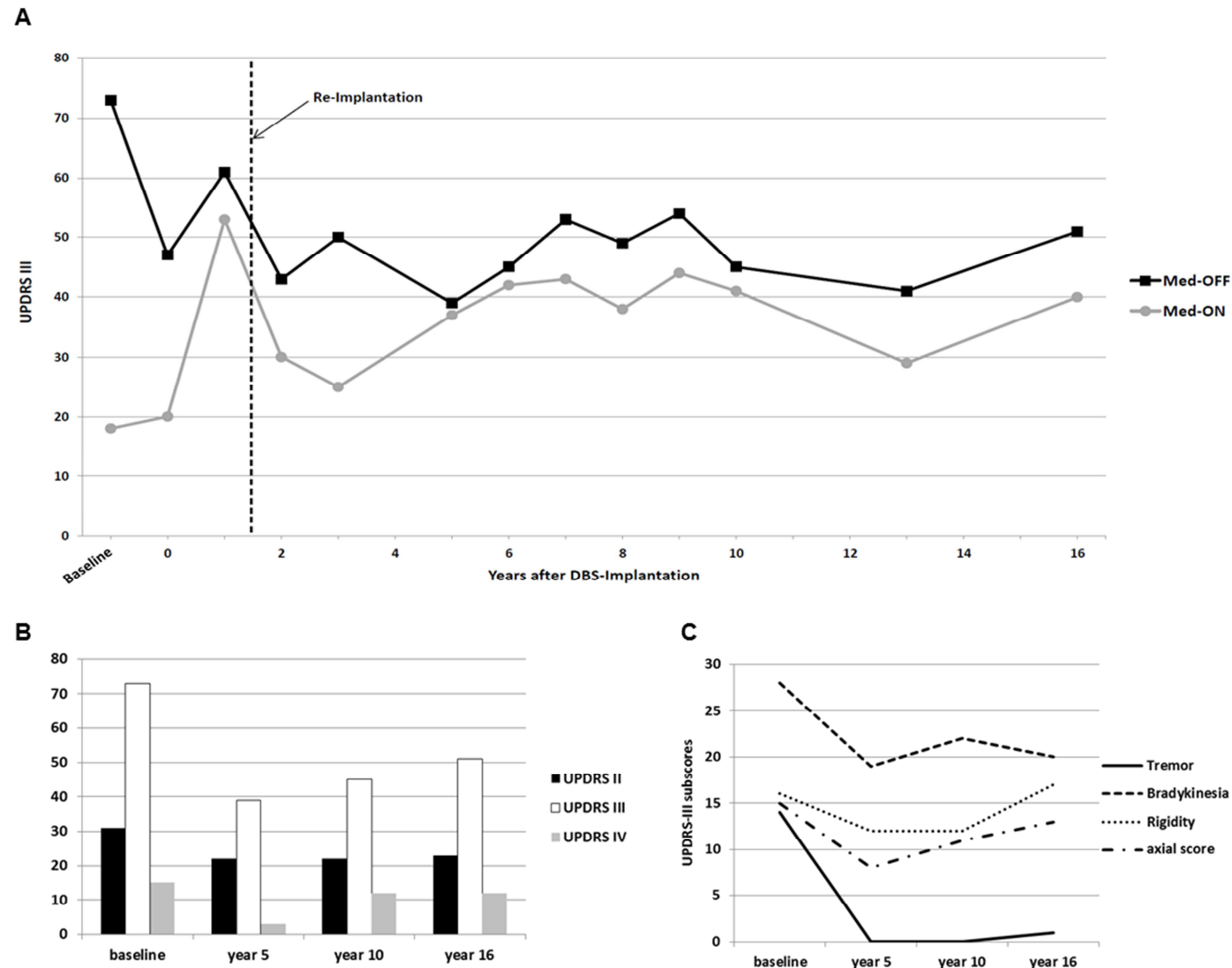


Figure 2. Case of longest follow up. Development of UPDRS- II-IV over a period of 16 years.

Highlights

- Pallidal DBS is effective in reducing parkinsonian motor signs
- Improvement of levodopa-induced motor complications and tremor by GPi-DBS can be sustained for more than 10 years.
- In a single case improvement of UPDRS-III (30%), UPDRS-IV (20%) and UPDRS-II (26%) was sustained for 16 years after GPi-DBS
- Beneficial effects on bradykinesia and rigidity might disappear within 5 to 6 years